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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/502,291	04/29/2005	Klaus Olaf Bornsen	ON/4-32325A	1850

1095 7590 08/11/2008

NOVARTIS
CORPORATE INTELLECTUAL PROPERTY
ONE HEALTH PLAZA 104/3
EAST HANOVER, NJ 07936-1080

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
08/11/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/502,291	BORNSEN ET AL.	
	Examiner	Art Unit	
	Deepak Rao	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,27-32,36 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *21,36 and 44* is/are allowed.

6)☒ Claim(s) *27-29,31 and 40-43* is/are rejected.

7)☒ Claim(s) *30 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the amendment filed on May 15, 2008.

Claims 21, 27-32, 36 and 40-44 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

1. Claims 40 and newly added claim 43 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating tumor of the brain, does not reasonably provide enablement a method of treating a proliferative disorder generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'the specification discloses that the claimed compounds possess activity as tyrosine kinase inhibitors and it is well known that tyrosine kinases are involved in cell proliferation and therefore, such compounds would be useful in treating diseases that result from uncontrolled cell proliferation'.

Applicant has not provided sufficient evidence that establishes that the disclosure would have enabled for one skilled in the art at the time of filing. It was clearly set forth in the previous office action that the instantly claimed therapeutic activity is generally unpredictable and highly structure specific area. Relevant portions from previous office action are provided below for convenience:

> The instant method includes all types of proliferative disorders including many types of cancers or tumors, some of which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.
>
> It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. In reference to cancer treatment using protein tyrosine kinase inhibitors, Traxler (Exp. Opin. Ther. Patents, 1997) stated that "pharmacological properties such as stability in biological media, bioavailability, metabolism or formulability are significant hurdles" see page 585, col. 2, lines 33-36. This is clearly indicative of the fact that the therapeutic role of these types of inhibitors is very speculative.
>
> The instant claims are drawn to 'a method of treating proliferative disease', which diseases include 'cancer'. No compound has ever been found to treat proliferative diseases or cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that, "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). A 'disease caused by proliferation of tumor cell' is anything that is caused by abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. Different types of cancers affect different organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers or proliferative diseases generally.
>
> Further, there is no established single antiproliferative therapeutic agent for all these types of diseases, which are characterized by the proliferation of tumor cells. The ideal chemotherapeutic drug would target and destroy only cancer cells without adverse effects or toxicities on normal cells. Unfortunately, no such drug exists; there is a narrow therapeutic index between cell kill of cancer cells and that of normal cells. Successful treatment of cancer requires elimination of all cancer cells, whether at the primary site, extended to local-regional areas, or metastatic to other regions of the body. The major modalities of therapy are surgery and radiotherapy (for local and local-regional disease) and chemotherapy (for systemic sites). For example, regarding the treatment of leukemia, The Merck Manual (online edition) states, that "Treatment

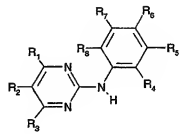
programs and clinical situations are complex". Dosage regimen is dependent on several risk factors and the contribution of each active ingredient of a multidrug combination therapy is complex and unclear. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, 'the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved'. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Traxler, in an article (Exp. Opin. Ther. Patents, 1997) stated that "The concept of the inhibition of growth factor receptor-mediated signal transduction via inhibition of its protein tyrosine kinase is a novel, **not yet proven** clinical approach to the regulation of cell proliferation", see page 585, col. 1. Therefore, the state of the art provides the need of undue experimentation for the instantly claimed therapeutic benefits.

Further, applicants have neither provided nor identified in the state of the art, a single class of compounds that can treat all types of proliferative diseases in a patient. Further, one skilled in the art of medicinal therapy recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to the carcinogenic process, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule. A detailed understanding of the molecular mode of action of the specific kinase, alongside the elucidation of the molecular pathology of individual diseases is required to identify disease types and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters to receptor response endpoints. Therefore, it is maintained that applicants have not provided sufficient test assays or data to support the claimed therapeutic method commensurate in scope, as of the filing date of the application.

2. Claims 27-29, 31, 41 and newly added claims 42-43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zimmermann, U.S. Patent No. 5,521,184. The reasons from the previous office action are incorporated here by reference.

Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant submits that 'Zimmermann indicates that pyridyl can be substituted by oxygen to form the N-oxide', however, argues that 'the reference teaches away from the claimed N-oxide compounds as the reference fails to disclose a single species of pyridyl N-oxide'.

As indicated in the previous office action, the reference teaches substituted pyrimidine compounds of formula (I) (depicted below for convenience):



(I),

wherein:

R_1 is unsubstituted or lower alkyl-substituted pyridyl bonded at a ring carbon atom and unsubstituted or substituted at the nitrogen atom by oxygen, i.e., pyridine N-oxide or N-oxido-pyridine;

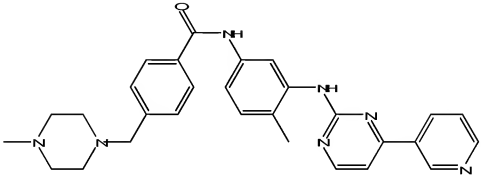
R_2 and R_3 are hydrogen;

one of R_4, R_5, R_6, R_7 and R_8 is a group of formula (II): $-N(R_9)-C(=X)-(Y)_n-R_{10}$

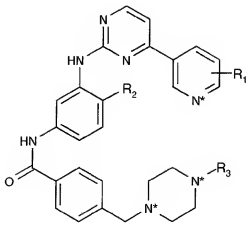
wherein R_9 is H, X is O, n is 0 and R_{10} is an aromatic radical (preferably phenyl) substituted by, for example, a 4-methyl-piperazinyl substituted lower alkyl;

and the remaining R_4, R_5, R_6, R_7 and R_8 are each hydrogen, lower alkyl, etc.

The reference further discloses several specific compounds falling within the above genus, see for example, the compound of Example 21, N-{5-[4-(4-methyl-piperazinomethyl)-benzoylamido]-2-methylphenyl}-4-(3-pyridyl)-2-pyrimidine-amine (structure depicted below for convenience):



The instant claim 27 is drawn to a compound of formula II (depicted below for convenience):



(II),

where R_1 can be hydrogen; R_2 and R_3 can be lower alkyl (e.g., methyl) and wherein at least one of the three nitrogen atoms marked by a star carries an oxygen atom.

As can be seen from the above, the instantly claimed compounds differ from the

reference disclosed compound of Example 21, by having an oxygen atom on one of the nitrogen atoms, e.g., the nitrogen atom of the pyridyl ring. The reference, however, teaches the equivalency of pyridyl and N-oxido-pyridyl as these are taught to be alternatives. The reference compounds are taught to be useful as pharmaceutical agents having protein kinase inhibitory activity. One of ordinary skill in the art would have been motivated to modify the reference disclosed compound by having a N-oxido-pyridyl in place of the pyridyl (as disclosed in Example 21), with the reasonable expectation of obtaining compounds having same activity and therefore, the same utility as taught for the reference compound. One of ordinary skill in the art in possession of the reference disclosed compounds, for example the compound of Example 21, with the disclosed therapeutic activity would have immediately recognized that, a single change in substitution such as replacing the pyridyl with N-oxido-pyridyl, can be done without the loss of the pharmacological activity. A single change in the reference disclosed compound would have resulted in a compound falling within the claimed structural formula II wherein one of the nitrogen atoms carries an oxygen atom. Accordingly, the reference contains sufficient teaching of the molecular modifications required to prepare the instantly claimed compounds.

The following rejections are necessitated by the amendment:

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 28-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following reasons apply:

1. Claim 28 recites the limitation **"with the proviso that** at least one of the three nitrogen atoms marked by a star carries an oxygen atom **if R_2 is methyl"** in lines 7-8. There is insufficient antecedent basis for this limitation in claim 27 on which claim 28 is dependent. The limitation in the base claim is independent of any other variables. Claim 27 recites that "at least one of the three nitrogen atoms marked by a star carries an oxygen atom", which is not dependent on the definition of R_2.
2. Claim 29 recites the limitation: "the stars indicate the nitrogen atoms which **optionally** carry an oxygen atom to form the corresponding N-oxides". This is not consistent with the base claim 27, wherein it is states that, "at least one of the three nitrogen atoms marked by a star carries an oxygen atom" and therefore, requires 'at least one N-oxide' where as the dependent claim indicates as an 'optional' limitation.

Allowable Subject Matter

Claims 21, 36 and 44 are allowed. Claims 30 and 32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications

may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Deepak Rao/
Primary Examiner
Art Unit 1624

August 12, 2008